A systems biology approach to understanding the efficiency of the lymph node in producing primed T cells

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***Short Abstract* — We developed a 3 dimensional agent based lymph node model with the organ structure and cell motion in accordance with biological data. We use this platform to analyze mechanisms that impacts lymph node function and shows potentiality in vaccination and disease treatment.**

I. Background

Dendritic cells (DCs) ingest foreign material (antigen) present during infection, process antigen for display on their cell surface, and migrate to T cell zones of lymph nodes (LNs) where millions of circulating T cells are present. A small fraction of these T cells (cognates) have receptors that bind to the displayed antigen on the DCs, initiating a cascade of events leading to priming. These primed T cells then return to the site of infection to lead the body's defense.

Recent studies employing two-photon microscopy[1] (2PM) have significantly advanced our knowledge of T cell motility and the behavior of cognate T cells in the presence of antigen-bearing DCs within LNs, but many unanswered questions remain. For example, it is difficult to relate the short length- and time-scale measurements of 2PM to efficiency of LNs in producing primed T cells.

II. Modeling and Analysis

We developed a 3 dimensional (3D) agent-based model representing the T cell zone of LNs, allowing for rapid *in silico* simulation of T cell zone function. We used the model to explore the effect of T cell zone morphology on LN efficiency and used uncertainty and sensitivity analysis to predict which mechanisms contribute significantly to the production of primed T cells.

A. Model construction

Monkey LNs were obtained, cross-sectioned, and fluorescently labeled to reveal the size and shape of T cell zones, density of T cells, and distributions of high-endothelial venules (HEVs) which serve as T cell entry and cortical and medulary sinuses which connects to efferent lymphatics (ELs) and serve as T cell exit ports, respectively. These data were used to build an agent-based model in C++ on a 3D toroidal lattice populated with T cells and DCs that interact according to prescribed stochastic rules.

B. Model calibration and validation

Values for system parameters were taken from the literature or otherwise calibrated with experimental data, (e.g., 2PM data of cell motion collected from live LN). T cells in model simulations exhibit motility in close accord with experimental data, moving at an average speed of about 13 μm/min with a motility coefficient of 45 μm2/min, and an average transit time of about 18 hrs.

Introduction of antigen-bearing DCs induces an *in silico* immune response, leading first to the production of effector CD4+ T cells followed by the production of effector CD8+ T cells.

C. Uncertainty and sensitivity analysis

System outputs were recorded and analyzed using uncertainty and sensitivity analysis[2]. We use Latin hypercube sampling (LHS) to sample from the parameter space. We then perform simulations using parameter sets generated by LHS, and calculated the partial rank correlation coefficients of simulation output with model parameters to determine the sensitivity. Results show that the cognate frequency of T cells and the lifespan of DCs after they are licensed by effector CD4+ T cells have a significant influence on T cell differentiation. Analysis of simulations also allows us to identify additional parameters that influence the output of effector cells from the LN, which is a marker of immune functionality during infection.

III. Conclusion

Our systems biology approach provides a platform not only to understand immune function, but also to guide manipulation of LN function in the context of infection.

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